View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by University of Huddersfield Repository

University of Huddersfield Repository

Atherton, John H and Hall, Alan

Scale-up – How do we get it right first time?

Original Citation

Atherton, John H and Hall, Alan (2011) Scale-up – How do we get it right first time? Chemistry Today, 29 (4). pp. 47-49. ISSN 0392-839X

This version is available at http://eprints.hud.ac.uk/13422/

The University Repository is a digital collection of the research output of the University, available on Open Access. Copyright and Moral Rights for the items on this site are retained by the individual author and/or other copyright owners. Users may access full items free of charge; copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational or not-for-profit purposes without prior permission or charge, provided:

- The authors, title and full bibliographic details is credited in any copy;
- A hyperlink and/or URL is included for the original metadata page; and
- The content is not changed in any way.

For more information, including our policy and submission procedure, please contact the Repository Team at: E.mailbox@hud.ac.uk.

http://eprints.hud.ac.uk/

John H Atherton

Scale-up
How do we get it right first time?

JOHN H. ATHERTON*, ALAN HALL
* Corresponding author
IPOS, University of Huddersfield, Queensgate, Huddersfield, HD1 3DH, United Kingdom

ABSTRACT

Scale-up in the context of fast moving process development can be problematic. Getting scale-up right requires an understanding of the way in which physical and chemical process parameters interact to determine overall performance. Multiphase systems are particularly difficult. The most common types of scale-up problem at the reaction stage will be shown, and the root causes will be discussed and exemplified. Common root causes are: increases in overall processing time on scale-up, with possible adverse effects on yield and quality; differences in heat transfer capability, which can feed back to increases in cycle time; changes in mass transfer rates, which can impact on reaction time and selectivity; poor dispersion of solids (mass transport), leading to low reaction rates and stalled reactions; and changes in mixing efficiency in homogeneous reactions, with implications for reaction selectivity. A procedure for identification of potential scale-up problems will be described.

INTRODUCTION

Increasing competitive pressures and the need to shorten development times has made the need for reliable scale-up ever more important. Published scale-up methods and are often heavily engineering biased (1), and assume a good knowledge of the chemistry, although some recent publications (2-6) explicitly recognise the need for multidisciplinary working.

Common manifestations of scale-up problems include: reactions slower than expected; selectivities poorer than expected; difficulties with solids handling; fouling or blockages; unexpected corrosion problems. Although cycle time and resultant productivity issues are important on scale-up, the most critical issues are usually around product quality and yield. Out-of-spec product can't be sold. For the chemistry to go wrong on scale-up, there must be some by-product forming reaction(s), and a key part of process development must be to understand both what these reactions are, and how imposed processing conditions will influence them. So the first thing to do in considering potential scale-up problems is to generate a picture of the chemistry, and to identify the branch points that lead to by-product formation. Then the related physical parameters should be added to the picture. An example is shown in Figure 1, in which the desired reaction is catalytic hydrogenolysis of the arylchloromethyl compound to give the corresponding methyl aromatic, and the major side reaction is a catalytic reductive dimerisation to give a diarylethane.

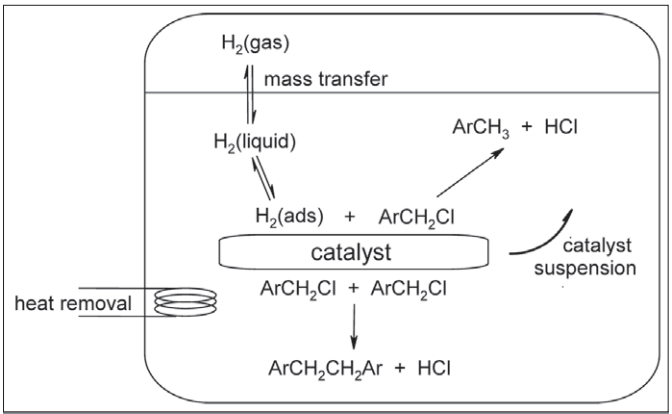

Figure 1. Representation of the chemical and physical processes involved in a hydrogenolysis process.

COMMON ROOT CAUSES OF SCALE-UP PROBLEMS

Time

Several factors contribute to increasing processing times on scale-up. Materials handling, charging procedures for solids and liquids, waiting times for analytical testing and delays due to manpower availability are all predictable and result in processing taking longer than at laboratory scale. More subtle are increases in cycle time caused by heat transfer issues. Figure 2 shows the decrease in heat transfer area/volume ratio as scale increases.

Thus, scale-up from I litre to 1,000 litres results in an order of magnitude decrease in the relative heat transfer surface

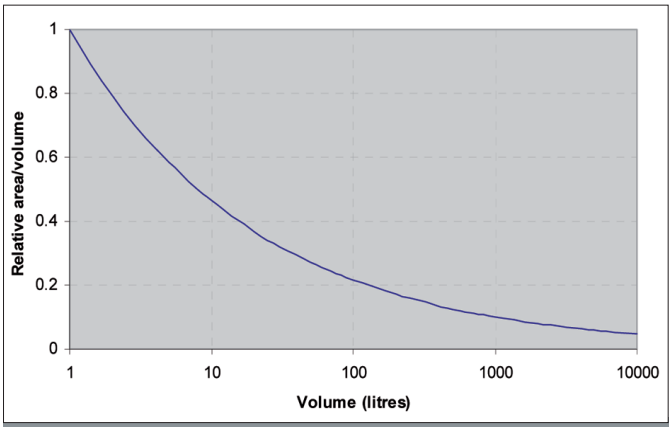

Figure 2. Relative heat transfer area/volume ratio vs. reactor volume.

area. Given similar heat transfer behaviour, this means that processes where the reaction time is limited by heat transfer will take around 10 times as long on scale-up. Although the time factor may be important, more significant may be the impact on chemical selectivity, if starting materials or products have limited stability over the increased reaction time. A recurrent theme in the authors' experience has been problems with processes involving distillation.

For example, distillative drying was being used to form the potassium salt of a phenol in solution in dimethylacetamide and xylene.

On the laboratory scale only one hour was required to remove the water and so drive salt formation to completion. At manufacturing scale the drying time was around 10 hours, and on this timescale significant hydrolysis of the dimethylacetamide solvent occurred, leading to the production of volatile dimethylamine and potassium acetate, with a reduction in the amount of the desired phenolate salt.

Heat transfer

Other problems caused by heat transfer issues arise from the use of more extreme temperature differentials between the reactor heat transfer surface and the batch. While the temperature of the bulk is unaffected, that of the process fluid in the film adjacent to the wall approaches that of the heat transfer surface. Where the heat transfer duty is heat input, this can result in decomposition of sensitive materials, or sometimes, in unexpected corrosion effects. When cooling is being applied, problems can occur when viscous materials are being used, because the low film temperature close to the heat transfer surface leads to a local increase in viscosity and consequently to a lower heat transfer rate. Cooling crystallisation processes can be a problem on scale-up if too low a surface temperature causes nucleation and precipitation on the heat transfer surface and consequent fouling.

Mixing

Many processes are carried out under "fed batch" conditions, usually to enable the reaction temperature to be maintained in the required range, but sometimes to avoid undesired side reactions due to local concentration transients, where a product can undergo a second reaction with the reagent being added (7). Highly exothermic reactions can generate high temperatures in the region of the mixing zone, and these may result in unwanted side reactions (8). A single question and experiment can be used to deduce the presence of a mixing problem:

– Would you expect a selectivity problem if you reversed the order of addition? During the mixing process there will be a transient excess of the component being added over the receiving reactant, so a concern over reversal of the order of addition requires investigation.
– Carry out the reaction on the laboratory scale with an agitator speed of around 1Hz. If this does not cause any degradation in performance versus the normal speed, then there is unlikely to be a problem on scale-up.

If the above give indications of a potential mixing problem, then detailed guidance is available (7).

Mass transfer

A majority of processes in the Pharma and Fine Chemicals area are multiphase (9). Some general purpose reactors, particularly at pilot scale, are not designed to process multiphase reactions. It is quite common to experience difficulty in adequately dispersing solid reactants. Potassium carbonate (10) and cesium carbonate (11) both have a published track record of causing problems in nonaqueous solvents. The dispersion of solid particles is dependent on particle size and density as well as on the vessel and agitator geometry. Hence careful attention to particle size specification and agitator design is necessary. Detailed guidance is available (12).

Gas-liquid reactions can also be problematic on scale-up. The commonly used gases hydrogen and oxygen both have solubilities in the millimolar region at atmospheric pressure, so the reaction solution will typically have to be resaturated hundreds of times in order to complete reaction at realistic process concentrations in excess of 1 molar. Best practice involves measuring mass transfer rate constants at laboratory and full scale, in order to ensure predictable scale-up (13).

Process conceptual analysis protocol

Getting process chemistry right requires an understanding of both the chemistry and the associated physical parameters that drive rate and selectivity. Chemists are good at the chemistry, less so at integrating the physics; chemical engineers can apply the physics, but often have difficulty in relating to the chemistry at an appropriate level. We have developed a protocol to assist in developing a good understanding of the physical and chemical factors that influence process performance. It requires input from a multidisciplinary group including chemists, chemical engineers and someone familiar with the full scale equipment. It is summarised in the 5 steps below:

1. Develop a picture of the chemistry of the reaction including desired and undesired reactions, and ionic processes that influence reactant availability, such as protonation of amines.
2. Add to the picture relevant physical processes – mixing, mass transfer, mass transport, heat transfer.
3. Acquire a diagram of the process equipment at both laboratory and full scale.
4. List the main physical variables:
   - time
   - heat transfer
   - mass transfer
   - dispersion of solids
   - mixing

   and common causes of problems:
   - side reactions
   - slow reactions
   - blockages
   - corrosion
   - solids handling
5. Interrogate the process step by step, questioning the relevance of physical variables and common problem areas at each stage.

Application of this protocol rarely fails to develop useful new insights into process performance.

Taking as an example the reaction picture in Figure 1, we see that both the desired reaction and the identified side reaction occur on the catalyst surface, and, whereas the desired reaction requires hydrogen the side reaction does not. Selectivity at this "branch point" is therefore influenced by the relative rates of access of hydrogen and starting material to the catalyst surface. Laboratory work with good hydrogen mass transfer gave high selectivity to the desired product. First attempts at scale-up gave unacceptable results, with slow reactions and significant amounts of the dimer. Temperature control was unsatisfactory, and increased temperatures favoured the side reaction. There are three critical duties of the reactor: to remove heat, to disperse gas, and to disperse the solid catalyst. The process was modified in three ways:

1. Hydrogen mass transfer was improved by optimising the vessel fill level, since gas entrainment was via the liquid surface,
2. The catalyst loading was reduced,
3. The reaction concentration was reduced,

leading to a satisfactory process (14). A similar approach has been reported recently to solve scale-up problems in the reduction of an imine (13).

CONCLUSIONS

Scale-up can be problematic in an environment where rapid introduction of new products is required. However, careful consideration of both the chemical and physical requirements and their interaction at large scale can help to avoid difficulties. A protocol is suggested involving a multi-disciplinary team with knowledge of the process and the equipment to be used. This can help to gain insights into likely problem areas based on an analysis of the physical variables and common causes of scale-up problems. ■

REFERENCES AND NOTES

1. A. Bisio, R.L. Kabel, *Scaleup of Chemical Processes*, John Wiley & Sons, 1985.
2. G. Caygill, M. Zanfir et al., *Org. Process Res. Dev.*, **10**, pp. 539-552 (2006).
3. F.L Muller, J.M. Latimer, *Proceedings of European Congress of Chemical Engineering (ECCE-6)*, Copenhagen Sept. 2007.
4. J.H. Atherton, K.J. Carpenter, *Process Development: Physicochemical Concepts*, OUP (1999).
5. I. Houson (ed.), Process understanding, Wiley-VCH (2011).
6. A.J. Blacker, M.T. Williams, (ed.) *Pharmaceutical Process Development: Current Chemical and Engineering Challenges*, pub. Royal Society of Chemistry, Cambridge (2011).
7. J.R. Bourne, *Org. Process Res. Dev.*, **7**, pp. 471-508 (2003).
8. J. Baldyga, J.R. Bourne et al., *Can. J. Chem. Eng.*, **17**, pp. 641-649 (1998).
9. J.H. Atherton, J.M. Double et al., paper presented to *World Congress of Chemical Engineering*, Glasgow 2005.
10. J.D. Moseley, P. Bansal et al., *Organic Process Research and Development*, **10**, pp. 153-158 (2006).
11. J. Leonard, *AZD6244: challenges of route design and development*, 28th SCI Process Development Symposium, December 2010.
12. E.L. Paul, V.A. Atiemo-Obeng et al., *Handbook of Industrial Mixing*, p. 546, Wiley-Interscience (2004).
13. K.M.J. Brands, S.W. Krska et al., *Org. Process Res. Dev.*, **10**, pp. 109-117 (2006).
14. J.H. Atherton, A. Hall, unpublished work.